As a preliminary matter, in response to the Notice to Comply (copy attached) relating to sequences, the Patent Office is requested to use the CRF from the parent file (09/441,315) to generate a CRF for the present application.

Claims 26-46 stand rejected under the judicially created doctrine of obviousness type double patenting in view of claims of 10-12 of U.S. Patent No. 5,602,301. Claims 47-68 stand rejected under 35 U.S.C. § 112, first paragraph. It is believed that the following remarks comprehensively address the rejections. Reconsideration and allowance of this application are therefore requested.

With regard to the rejection of claims 26-46 for double patenting, enclosed with this response is a Terminal Disclaimer in respect of U.S. Patent No 5,602,301, to obviate this rejection. Entry of the Terminal Disclaimer and withdrawal of this rejection are solicited. In addition, applicant would like to inform the Examiner that this '301 patent is the subject of a pending reexamination proceeding, No. 90/006,098, filed August 28, 2000.

With regard to the rejection of claims 47-68 under 35 U.S.C. § 112, first paragraph (enablement), the applicant respectfully traverses this rejection because the specification enables these claims. The question raised by this rejection is whether the specification enables a reasonable number of species across the scope of the claims. It is submitted that the specification does, and accordingly that the rejection should be withdrawn.

The applicant has discovered that myocardial tissue can provide a stable grafting bed for cardiomyocytes. That having been done, and in view of the further teachings in the application, and the state of the art as of the priority date of this

application, a large number of species is enabled for treating diseased or damaged myocardial tissue using the cellular grafts recited in these claims.

The present application teaches not only with general discussion but also with highly demonstrative, successful specific working Examples. In Example 1, applicant demonstrates the generation of a stable graft by implanting AT-1 cardiomyocytes into myocardial tissue. Example 2 provides an illustrative dosage of cells for an injection (4-10 x 10^4). Example 2 also expressly notes that long-term viable grafts were established, that the engrafted cells were directly juxtaposed to host cells, and that no deleterious effects were observed from the graft.

Example 3 also demonstrates the generation of a stable graft of cardiomyocytes. In this example 1-10 x 10^4 cells isolated from embryonic hearts were injected. As reported, the grafted cardiomyocytes were juxtaposed directly with host cardiomyocytes, and furthermore were coupled to host cardiomyocytes through junctional complexes. Again, no deleterious effects were observed from the grafts.

In addition to these specific Examples provided, the specification discloses the utilization of cells genetically modified to express a number of other useful substances, teaching:

> ...angiogenic factors (as exemplified by Basic and Acidic Fibroblast Growth Factors; Transforming Growth Factor-Beta, Vascular Endothelial Growth Factor and Hepatocyte Growth Factor) to induce neovascularization. Similarly, grafts expressing neurotrophic agents near an infarcted region may

be used to ameliorate the arrhythmogenesis associated with the border zone. These and other candidate substances for targeted delivery to heart will be apparent to those skilled in the area.

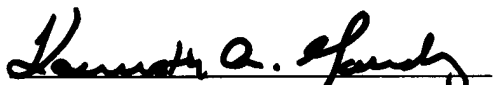
Even further, and more generally, in considering the issue of enablement in the instant case, it must be borne in mind that the claims are directed to cellular engraftment, in which disease-free, damage-free cells can be introduced into tissue otherwise containing diseased or damaged cellular tissue. The ability, within the scope of the present claims, to deliver such cells to provide non-diseased, non-damaged cells, where only diseased or damaged tissues otherwise exists, presents a broad level of enablement for treating diseased or damaged myocardial tissues. This is simply not a case where one has to necessarily induce a change in diseased or damaged cells in order to achieve a beneficial effect with genetically modified or unmodified engrafted cells, nor do the claims require a systemic response throughout the patient to provide treatment.

In summary, it is submitted that a reasonable correlation exists between the scope of claims 46-68 and the scope of enablement provided by the specification. It is thus requested that the rejection of claims 46-68 be withdrawn.

New claim 69 and claims 70-73 dependent thereon have been added to the application. These claims introduce no new subject matter. Claim 69 is identical to independent claim 48, except that it specifies the treatment of infarcted myocardial tissue. It is believed that claims 69-73 are allowable, at the least, for the reasons discussed above. Favorable consideration of these claims is therefore requested.

In view of the foregoing amendments and remarks, reconsideration and allowance of this application containing claims 26-73 is requested. The Examiner is also requested to contact the undersigned by telephone if such may be useful in expediting the allowance and issuance of any or all of the claims pending in this application.

Respectfully submitted,

By: 

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ATTACHMENT SHOWING CLAIM CHANGES

39. (Amended) A method for cellular grafting according to claim 26, wherein said cellular graft comprises cardiomyocyte cells intercellularly coupled to cardiomyocyte cells of said myocardial [issue] tissue by junctional complexes.

47. (Amended) A method of treating diseased or damaged myocardial tissue in an animal comprising forming a graft of cardiomyocyte cells in said tissue, wherein the graft is viable for at least six months.

69. (New) A method for treating infarcted myocardial tissue in an animal, comprising forming a graft of cardiomyocyte cells in said tissue, wherein said graft is viable for at least six months.

70. (New) A method for treating infarcted myocardial tissue of claim 69, wherein the myocardial tissue is ventricular myocardial tissue.

71. (New) A method for treating infarcted myocardial tissue of claim 70, wherein the myocardial tissue is left ventricular myocardial tissue.

72. (New) A method for treating infarcted myocardial tissue of claim 69, wherein the animal is a mammal.

73. (New) A method for treating infarcted myocardial tissue of claim 71, wherein the animal is a mammal.

Application No. 09/878,011

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing" OR REQUEST TO USE CRF FROM PARENT APPLICATION.

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.